



Sleep disturbances and Alzheimer's disease: a multiscale approach from exposome to neurobiology and precision medicine

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Abstract Sleep disturbances and Alzheimer's disease (AD) are interconnected public health challenges. However, the underlying mechanisms of their complex relationships remain elusive. Here, we propose a hypothetical integrative, stream-like model outlining how external and internal exposome factors accelerate brain aging, thereby exacerbating circadian dysregulation, orexin-mediated hyperexcitability, metabolic imbalance, and inflammaging. These changes can lead to increased sleep fragmentation and reduced slow-wave sleep, triggering widespread neuroinflammation, glymphatic dysfunction, and the

accumulation and dissemination of beta-amyloid and tau peptides. These processes collectively accelerate synaptic dysfunction, neuronal loss, and cognitive decline. We also highlight recent neuroimaging evidence that elucidates the neural substrates underlying the relationship between poor sleep and AD. Moreover, tackling their shared burden necessitates the active consideration of inter-individual variability in vulnerable populations through artificial intelligence and computational approaches, aligning with the core tenets of precision medicine. We hope this review encourages clinicians to prioritize monitoring and

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treating sleep disturbances to reduce the incidence, severity, and consequences of dementia in the general population.

Keywords Sleep disturbance · Alzheimer's disease · Tau · Amyloid · Exposome · Precision medicine

Introduction

The global prevalence of sleep disturbances in community-dwelling older adults is substantial. Among them, obstructive sleep apnea (OSA) (46.0%) is the most prevalent, followed by poor sleep quality (40.0%), other sleep disturbances (37.0%), insomnia (29.0%), and excessive daytime sleepiness (19.0%) [1]. These conditions are also frequently reported in patients with Alzheimer's disease (AD) [2, 3] and rising driven by population aging, growing demands of the 24/7 rhythm [4], physical and social environmental changes [5, 6], widespread socioeconomic disparities affecting brain aging [7], and pervasive modern public health challenges, including physical inactivity, obesity, and cardiometabolic diseases [8, 9, 10].

Sleep disturbances and AD have a complex inter-relationship [11–13]. Converging evidence from animal and human studies indicates that poor sleep may facilitate the transition from asymptomatic to clinical AD [14–21]. Longitudinal studies identified a robust association between abnormal sleep duration, reduced sleep efficiency, and attenuated slow wave sleep (SWS), which in turn was associated with an increased risk of cognitive impairment [22–25], neurodegenerative pathological deposition, and dementia up to 40 years later [26–28]. Notably, a longitudinal study of approximately 8,000 individuals suggested that short sleep duration (<6 h) in midlife (e.g., ages 50–60) is associated with a 30% higher risk of incident late-life dementia, independent of sociodemographic, behavioral, cardiometabolic, and mental health factors [25]. A meta-analysis across 35 longitudinal studies [29] and another one based on 60 studies [30] found that various forms of sleep disturbances, such as insomnia, sleep-disordered breathing (SDB, including OSA, sleep fragmentation, and sleep-related movement disorders, were associated with a higher risk of developing AD and other forms of dementia. It has also been shown that for

each percentage decrease in SWS per year, there was a 27% increase in dementia risk 17 years later [26]. A histopathological study of deceased 90+ year olds showed that longer subjective sleep duration 40 years prior to death was associated with lower burden of amyloid- β (A β) plaques and TAR DNA-binding protein 43 (TDP-43) pathology at death [27]. Thus, poor sleep health should be considered a crucial risk factor for developing cognitive decline associated with AD [11, 14, 18], which can be modifiable through proper sleep-targeted treatments [31–34]. Beyond its role as a (modifiable) risk factor in the preclinical stage, sleep disturbances are also a common symptom in clinical AD. Previous meta-analyses found that patients with AD regularly complain of poor sleep [2, 35], with many exhibiting a higher rate of OSA or insomnia symptoms [3, 36]. Another meta-analysis based on polysomnography studies showed that AD patients exhibited marked reductions in total sleep time, sleep efficiency, SWS bouts, paired with a higher rapid eye movement (REM) sleep latency, wake time after sleep onset (WASO), and total number of awakenings. Interestingly, lower SWS and REM sleep duration were associated with higher cognitive impairment in AD patients [37]. Therefore, these pieces of evidence point to a distinctive, inter-dependent, and bidirectional relationship between sleep disturbances and AD pathology. However, the precise neurobiological mechanisms that define this relationship remain to be further elucidated.

To provide a general overview of the complex interplay between sleep and AD, it is imperative to consider a wide range of factors, including genetic, exposome, psychological, and neurobiological factors, across several research strands [38]. Whereas previous synthetic reviews have favored a reductionist approach, highlighting key components (e.g., aging, A β , tau, circadian dysregulation, glymphatic dysfunction) [11, 14–17, 21, 39, 40], this work updates the field by synthesizing a stream-like model that integrates various bio-psycho-social factors involved in the initiation of AD pathophysiology, informed by recent evidence. The 13th-century Persian poet Rumi illustrates the importance of this holistic approach to complex problems in his story, “Elephant in the Dark.” In this story, a group of people is brought into a dark room to see an elephant for the first time. As they could not see it as a whole, each person described it as a snake, fan, wall, column, or rope,

based on their prior knowledge and what they could feel at that moment. All of them insisted their perspective was correct, yet none understood the whole of the beast. A similar problem arises when attempting to understand the sophisticated interplay between sleep and AD. As mentioned above, the nature of their relationship can differ drastically depending on the form of sleep disturbance and the manifestation of dementia. Hence, it is essential to adopt a holistic perspective on phenomena as complex and mutable as the relationship between sleep and AD. Furthermore, individual variability in pathophysiological and symptomatologic profiles remains a substantial obstacle in developing reliable biomarkers and effective therapeutic strategies. Given these heterogeneity challenges, our work also discusses how artificial intelligence and advanced machine learning can contribute to our understanding of this variability and enable predictions at the individual level from a personalized medicine perspective. Finally, our work underscores the translational implications of conventional and novel sleep-targeted therapeutic approaches in reducing the conversion rate of asymptomatic conditions to AD. Taken together, we aimed to highlight the genetic and exposome risk factors that contribute to both sleep and AD, the neurobiological mechanisms underlying their interplay, and recent approaches to mitigate this risk through precision medicine lens.

An integrative stream-like model on how sleep disturbances may exacerbate AD pathophysiology

Our hypothetical integrative stream-like model (Fig. 1) suggests that specific genetic, lifestyle, environmental, and psychological factors exacerbate brain aging processes in vulnerable individuals [5–7, 15, 24], leading to more suprachiasmatic dysfunction, circadian dysrhythmia, metabolic dysregulation, inflammaging (i.e., chronic, low-grade inflammation associated with aging), and orexin hyperexcitability [16, 34, 41, 42]. These changes further induce sleep fragmentation, decreased slow wave sleep, increased production, accumulation, and dissemination of toxic misfolded brain proteins (i.e., A β and tau peptides) [19, 20], and prevent physiological waste clearance through the glymphatic system [17]. The glymphatic pathway has been suggested to clear such peptides, mainly during SWS, by active fluid transport

from the interstitial space through the aquaporin-4 (AQP4) water channels in astrocyte end-feet, which are severely affected by age and may lead to A β and tau retention [17, 43–45]. Notably, it is under debate whether brain clearance is increased [43, 46] or decreased [47] during deep sleep, and whether sleep disruption induces increased production of A β and tau [19, 20], or if glymphatic failure is responsible for the greater retention and accumulation of A β and tau, or a combination of both [48, 49] (*see Sect. "Waste clearance via the glymphatic system" for more details*). It is well documented that A β and tau accumulation lead to increased oxidative stress, astrocyte and microglial activation, and widespread neuroinflammation [50, 51]. It has been shown that the accumulation of tau (e.g., in the hippocampal formation) specifically reduces GABAergic interneurons, which contribute to disinhibition-like changes, promotes astrogliosis, alters synaptic plasticity, and together results in metabolic changes in the hippocampus and memory decline [52–54]. Impaired homeostasis (rest-activity rhythm fragmentation) also leads to hyperexcitability, hyperarousal, and subsequent sleep fragmentation in AD [55]. These changes disrupt sleep oscillation coupling and continuity of sleep–wake patterns, which in turn further exacerbate A β and tau aggregation throughout the entire brain, leading to progressive synaptic dysfunction and degeneration, brain networks' reorganization, reduced white matter integrity, neuronal loss, cognitive impairment, and finally, conversion to dementia due to AD [11, 21, 40, 52, 53]. In the following sections, we will discuss the sleep-AD interplay from different angles.

Aging impacts on the link between sleep and AD

Sleep patterns change in numerous ways as people age. Multiple sleep disorders become more common, including insomnia disorder, SDB, restless legs syndrome, and REM sleep behavior disorder (RBD) [3, 56–58]. This increase in prevalence occurs for several reasons, including changes in body composition, presence of age-related medical comorbidities, upper airway anatomy, and muscle function in the case of SDB [59], changes in medical and psychiatric comorbidities, frailty and disability, and circadian rhythm disturbance in the case of insomnia [58, 60], changes in iron and dopamine signaling in the case

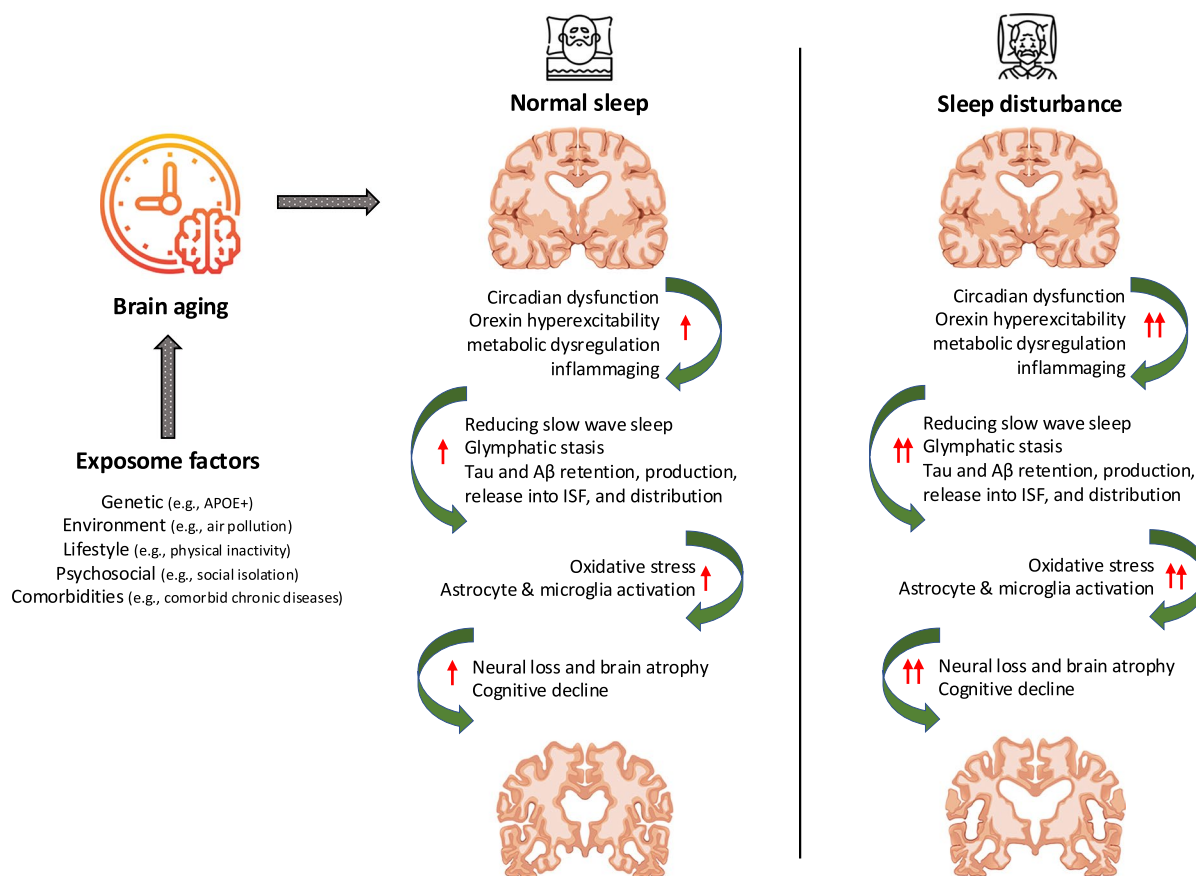


Fig. 1 Schematic image of the cascade of stream-like events linking sleep, aging, and brain atrophy in subjects with normal sleep vs. sleep disturbances. Brain aging disrupts the circadian rhythm and sleep–wake pattern, leading to mild brain atrophy in individuals with normal sleep patterns. However, in some vulnerable subjects, due to particular genetic, environmental, psychosocial, lifestyle, and neuropsychiatric comorbidities,

sleep disruption is more prominent, which robustly reduces slow wave sleep and increases glymphatic stasis. These alterations induce the accumulation and distribution of A β and tau, which leads to astrocyte and microglial activations and neuro-inflammation that further disrupt sleep patterns, triggering a vicious cycle that exacerbates disease progression

of restless legs syndrome [61], and early stage emergence of a synucleinopathy in the case of RBD [62]. It is essential to note, however, the high inter-individual variability in the effects of age on sleep disorders, which are more prevalent in the presence of multiple medical comorbidities, suggesting that poor sleep is not necessarily an inevitable consequence of aging [63]. This means that comorbid age-related diseases may also be critical risk factors for the development of sleep disturbances that impact dementia risk. For example, obesity, type 2 diabetes, renal dysfunction, stroke, congestive heart failure, chronic obstructive pulmonary disease, and depression, all which increase in prevalence with age, either increase risk

of developing OSA or magnify the effects of OSA on health outcomes [64]. Depression and insomnia disorder have also been shown to be risk factors for each other [65, 66], and many other age-related conditions and their treatments are associated with sleep disruptions, including chronic pain, cancer, heart diseases, respiratory diseases, gastrointestinal diseases, neurodegenerative diseases, and psychiatric illnesses [67, 68]. In these cases, treatment of comorbidities and careful evaluation of comorbidity treatment and its potential impact on sleep should be a critical part of the sleep treatment plan.

In addition to comorbidities, emerging evidence indicates that sex differences in sleep disturbance

become increasingly pronounced with aging, which may explain the higher burden of AD in women [69]. In a 12-year cohort of middle-aged adults, women experienced greater deterioration in sleep quality, latency, and efficiency compared with men, which was most evident in premenopausal women [70]. The prevalence of insomnia is also higher in older women than in older men, and women are more likely to experience multiple insomnia symptoms [71]. In contrast, other forms of sleep disturbance, including increases in SDB prevalence and shorter SWS duration, are more pronounced in older men than older women [72]. Sex differences in OSA expression, partially explained by differences in endotypes, result in more REM-dominant expression of hypoxemia in women [73]. Recent work from multiple cohorts has shown that hypoxemia during REM sleep may be particularly relevant for the vascular, degenerative, and cognitive consequences of OSA [74–76]. The reduction of sex hormones in older age and glial reactivity contribute differently to the development of amyloid burden in women than in men [77, 78]. A recent multi-omics study, based on data from one million individuals, demonstrated the existence of female-specific pathways, including amyloid, neurite, stress, clearance, and immune processes, with genes enriched for expression in microglia and astrocytes [79], which aligns with evidence of glymphatic impairment and neuroinflammation in AD. Taken together, these findings suggest that aging women face a convergence of increased sleep disturbance, hormonal fluctuations, and neurodegenerative vulnerabilities, highlighting the necessity of sex-specific strategies in precision medicine for AD. However, it remains understudied to what degree sex differences in sleep disturbance in older age contribute to sex differences in AD.

Global changes in sleep architecture and local changes in sleep oscillation dynamics have been reported. At the level of sleep macroarchitecture, sleep fragmentation, sleep onset latency, and WASO increase; SWS, total sleep time, and sleep efficiency decrease; and REM sleep latency advances [80]. In the absence of sleep disorders, other neuropsychiatric disorders, or a neurodegenerative process, older adults exhibit minimal loss of REM sleep [81], indicating that non-rapid eye movement (NREM) sleep expression may be more sensitive to normative aging than REM sleep expression. Some cross-sectional

evidence suggests that SWS declines are nonlinear across the adult lifespan, being maximal in midlife and minimal or stable after midlife [82]. However, longitudinal evidence indicates that SWS continues to decline past the age of 60 in cognitively unimpaired older adults, in contrast to the relative stability observed in REM sleep [26]. This is consistent with longitudinal data from a different study, which showed continual reductions in NREM SWA after midlife [83].

Characteristic changes in the way the brain locally expresses NREM sleep oscillations, including the loss of cortical slow waves and cortico-thalamic sleep spindles, are consistently observed in aging studies [15]. One study utilizing data from the Sleep Heart Health Study reported longitudinal changes over ~5 years in spectral power across frequencies during both NREM and REM sleep in over 2,000 older adults aged 39–86 years old [83]. The two significant decreases in spectral power during NREM sleep were within the slow wave and sleep spindle frequency ranges. There was one notable exception to this longitudinal age effect: <1 Hz SWA, the frequency range of the slow oscillation (SO) [84], showed increases in both midlife and older age. This is consistent with some cross-sectional studies of aging, which show a decrease in the average frequency of slow waves [85] and greater relative reductions in delta activity than SO power [86]. An intriguing feature of the latter finding is that there appears to be a sex effect on how the SO changes with age, with SO power increasing in women and decreasing slightly in men [86]. This mirrors the sex effect in SWS observed in cross-sectional studies, where women exhibit more preserved SWS, while men show clearer declines. Interestingly, longitudinal decreases in spectral power during REM sleep are not apparent with age, only increases in low-frequency (<2 Hz) delta activity, theta activity, and alpha activity, with these increases being more prominent in women than men [83]. The functional significance of these age-related changes in REM sleep microarchitecture remains unclear, but further highlights the differences in age effects on NREM versus REM sleep. An equally important finding was the significant individual variability in the longitudinal change in NREM spectral power, demonstrating that, as with sleep microarchitecture, deficits in sleep oscillations may also not be an inevitable part of aging.

While the effects of aging on sleep expression have been thoroughly characterized, the mechanisms underlying these changes remain unclear. Dysfunction and degeneration within the subcortical circuit regulating sleep and wake brain states are contributing factors. Studies in rodents and humans have reported associations between sleep fragmentation and degeneration of galanin-expressing sleep-promoting inhibitory neurons in the intermediate nucleus, hyperexcitability in orexin-expressing wake-stabilizing neurons in the lateral hypothalamic area, and degeneration in catecholaminergic wake-active neurons in the ascending arousal system, including those within the noradrenergic locus coeruleus [87]. One proposed mechanism for this is endoplasmic reticulum stress and dyshomeostasis within orexigenic and noradrenergic sleep–wake regulating nuclei, which increases with age and contributes to neuronal injury and neurodegeneration [88]. In this study, older rodents showed a reduced c-fos response to wakefulness within orexigenic hypothalamic and noradrenergic locus coeruleus neurons compared to younger rodents. Both wake-promoting neuronal populations show high unfolded protein response (UPR) burden even in young rodents, resulting in phosphorylated-protein kinase RNA-like endoplasmic reticulum kinase (p-PERK) immunoreactivity, a marker of compensated ER stress. The percentage of these neurons expressing p-PERK immunoreactivity doubled in older rodents, leading to proapoptotic signaling and increased activation of CCAAT-enhancer-binding protein homologous protein (CHOP) and Growth Arrest and DNA Damage-Inducible Protein 34 (GADD34) markers of ER dyshomeostasis that were relatively sparse in younger rodents. This shift from compensated to uncompensated ER stress in response to increasing UPR burden could ultimately result in the increased neuronal injury and dysfunction observed in these nuclei with age. While these findings do not preclude similar processes being present in other wake-promoting nuclei, including the suprachiasmatic nucleus, they are noteworthy, as orexin expressing neurons in the lateral hypothalamic area and noradrenergic expressing neurons in the locus coeruleus are considered to be among the first nuclei in the brain impacted by tau pathology, with inclusions observed as early as Braak stage [88, 89]. Endoplasmic reticulum stress can trigger neuroinflammation and be triggered by it [90], and

neuroinflammation rises with aging and is thought to contribute to age-related disease progression, including in neurodegenerative diseases [91]. These neuro-inflammatory processes may underlie early tau inclusions in these wake-promoting nuclei, driving early changes in sleep/wake homeostasis (*see* Sect. "[Neuroinflammation](#)" for details).

The consequences of these age-related changes in sleep are multifaceted. Increased sleep disorder prevalence appears to directly contribute to oxidative stress, inflammation, cardiovascular and cardiometabolic diseases, mood disorders, cognitive decline, and the number of dementia patients [35, 92–97]. The presence of OSA, which results in sleep fragmentation and repeated intermittent hypoxemia, triggers vascular endothelial dysfunction, inflammation, and oxidative stress. For example, expression of endothelial nitric oxide synthase (eNOS) and its activated, phosphorylated form, P-eNOS, essential regulators of blood vessel dilation, were reduced by 59% and 94% relative to controls, while nitrotyrosine and cyclooxygenase-2 (COX-2), markers of oxidative stress and inflammation, respectively, were 5 times higher in patients. All of these effects were reversed after 4 weeks of recommended adherence to continuous positive airway pressure (CPAP) therapy [93]. These effects are likely not specific to OSA, as age-related increases in sympathetic nervous system tone, associated with autonomic nervous system dysregulation [98], may be exacerbated by sleep fragmentation and restriction, hypoxemia, and insomnia-associated hyperarousal [99], and may represent a core mechanistic feature driving increased oxidative stress, impaired endothelial antioxidant responses, chronic inflammation, and metabolic dysregulation observed in all these forms of age-related sleep disturbances [93, 100, 101]. Indeed, even acute sleep restriction elevated nuclear factor (NF)- κ B, a molecular marker of a pro-inflammatory signal cascade [102]. Many of these mechanisms, alongside metabolic hormone dysregulation, contribute to disruptions in metabolic homeostasis and impaired cardiometabolic health as well [103]. The co-occurrence of age-related increases in sleep disturbance and inflammation is even relevant for mood disorder risk. A randomized clinical trial in adults over 60 demonstrated that experimental induction of inflammatory exposure resulted in a threefold increase in depressive symptoms in patients with insomnia compared to patients

without insomnia [104]. The association between inflammatory cytokines and depressive symptoms was significant only in the insomnia patient group, suggesting that links between inflammation and mood disorders may depend on the presence of sleep disturbance. Collectively, these age-related disruptions of sleep may thus create a vicious cycle that promotes the acceleration of molecular processes triggering macroscale AD pathogenesis.

Exposome factors

The 3P model, which consists of predisposing, precipitating, and perpetuating factors, developed initially to assess insomnia etiologies [105], can be applied to various neuropsychological conditions, including AD [38]. It provides a framework for understanding the role of biological, psychosocial, and environmental constructs in disease development, maintenance, and treatment. The *predisposing factors* are long-lasting conditions that occur in the premorbid phase of the disease, such as genetic vulnerability, female sex, aging, hyperarousal (e.g., due to overactivity of the hypothalamic–pituitary–adrenal system), a positive family history, underlying chronic diseases, and specific personality traits make individuals vulnerable to developing a clinical condition such as insomnia disorder [106, 107]. The *precipitating factors* can be single, multiple, or recurrent events, including environmental or psychosocial factors that induce stress (e.g., family-related stress, shift work, job loss, or the loss of a loved one), as well as chronic medication use that affects sleep patterns. Although acute precipitating factors usually resolve over time through natural adjustment processes, some individuals develop maladaptive habits or coping strategies that can lead to classical conditioning and the maintenance of sleep disturbances. These *perpetuating factors* include behavioral changes due to the progression of insomnia disorder (e.g., sleep-related negative pre-occupation, pre-sleep arousal, dysfunctional beliefs, and rumination) [108, 109]. Similarly, the AD exposome model suggests that there are various interactive macro-level physical or social factors (e.g., air pollutants, rural/lifestyle/urban and sociodemographic factors) and individual endogenous/psychological factors (e.g., diet, obesity, smoking, infections, physical activity, stress), which collectively increase dementia

risk, especially in the presence of the Apolipoprotein E (APOE) $\epsilon 4$ allele [6, 7, 110, 111]. Recently, Ibanez and colleagues highlighted the importance of the *One Health* global approach, assessing the role of internal (e.g., genetic, neuroinflammation), physical (e.g., air pollution, microplastics), and social exposome (e.g., sociodemographic disparities, stress) factors on brain health, aging, and dementia [7, 112, 113]. Next, we will discuss the genetic, lifestyle, and environmental factors that can impact both sleep health and the progression of AD.

Genetic factors

There is well-documented evidence that APOE is a key genetic risk factor for late-onset sporadic AD [114]. Some evidence also suggests that the presence of the APOE $\epsilon 4$ allele is linked to a higher risk of developing sleep disorders, such as OSA [115, 116]. Healthy older individuals carrying the APOE $\epsilon 4$ allele showed various forms of objective sleep disturbances using actigraphy and PSG, but their subjective sleep quality was not correlated with the presence of the APOE $\epsilon 4$ allele, suggesting that objective sleep disruption may precede subjective reports of disturbance in subjects at increased risk for dementia [117]. However, a post-mortem study indicated that although APOE $\epsilon 4$ homozygosity was associated with sleep disturbance, such a relationship is independent of AD pathology and cognitive status [116]. Besides APOE $\epsilon 4$, the ABCA7 mutation is strongly linked with late-onset AD in African Americans [118]. The high-risk carriers of ABCA7 who reported poor sleep quality exhibited impaired learning, suggesting that high sleep quality may be neuroprotective against the genetic risk of AD [119]. A genome-wide association study (GWAS) based on self-report and accelerometer-measured sleep traits from UK Biobank (UKB) data did not find strong evidence to support a causal effect of sleep genetic traits on AD [120]. However, other GWAS studies using UKB observed an association between higher polygenic risk scores for AD and short sleep in middle-aged populations [121]. This study found that AD genetic risk influences sleep duration prior to the onset of dementia. Thus, abnormal sleep duration could be considered an early marker of AD [121]. It has been demonstrated that polygenic risk scores for sleep duration mediate the link between sleep duration, mental health, and

cognitive performance [24]. A Mendelian randomization study based on three big datasets, found that AD may causally affect sleep patterns, such as morning chronotype, shorter sleep duration, reduced insomnia, and fewer sleep episodes. However, the study did not identify a causal role for disturbed sleep patterns in the development of AD [122]. Thus, the current evidence indicates that genetic AD traits have a causal effect on sleep health, even before the ages when AD pathology begins to accumulate. This suggests that sleep disturbances may be an early indicator of AD pathophysiology.

Environmental, psychosocial, and lifestyle factors

The key role of exposome factors in the prevention and management of both dementia and sleep disturbances has been highlighted previously. For example, climate change (higher temperatures and severe weather events) is associated with poor sleep health [123, 124] and increased risk of dementia [125, 126]. Moreover, air pollution exposure is linked with the onset and progression of cognitive decline and AD, due to inducing systemic and neuroinflammation, increasing the metal load in the brain, abnormal respiratory/cardiovascular systems, and sleep disturbance, which impairs glymphatic waste clearance [111]. Another study based on the community-dwelling population observed that lower vegetation density and higher air pollution were associated with altered brain structure in the limbic network, cognitive impairment, and maladaptive psychosocial functioning [127]. On the other hand, higher neighborhood walkability, green space, and tree canopy were associated with better cognitive performance [128]. Thus, urban environment plays a critical role in shaping cognitive trajectories and brain aging, particularly in older adulthood [113, 129].

In addition to environmental factors, better educational access across the general population is associated with increased cognitive reserve, serving as a protective factor against cognitive decline and brain aging by providing greater awareness of cerebrovascular health and the consequences of neurodegeneration [130, 131]. A 20-year study demonstrated that higher education delays cognitive decline for up to 7 years before the exacerbation of AD pathology. Likewise, sleep hygiene education and prioritizing sleep are pivotal factors

in promoting healthy sleep behaviors [132]. Lower socioeconomic status, driven by less household income, educational attainment, and unstable employment status, is associated with a higher risk for AD, moderated by biological age as measured by leucocyte telomere length [133]. Congruent with these findings, an early US-based survey found that individuals with higher income and education levels had better sleep efficiency, and African American men had less sleep duration than other race or sex groups [134]. A meta-analysis of the sleep profiles of 134,874 children (aged 6–9 years) from 24 countries demonstrated that low family-perceived wealth, contrary to low parental education, was associated with shorter nocturnal sleep time (<9 h) across these countries [135]. Large-scale cross-country sleep assessments also found that nocturnal sleep was shorter and had a later onset in East Asia compared to Europe and the US, suggesting a cultural difference in coping with inadequate sleep, variations in working hours culture, socioeconomic status, and geographic latitude [136, 137]. Interestingly, shorter sleep hours were associated with worse spatial navigation in older adults across 63 countries [137].

The key impact of lifestyle on sleep disturbance and brain health is evident. The FINGER study conducted a longitudinal, multidomain clinical trial and found that modifying lifestyle factors, such as diet, exercise, cognitive training, and vascular risk monitoring, can prevent cognitive decline in older adults [138]. Similarly, sleep health is negatively associated with poor diet (e.g., fast-food or high sugar consumption), irregular daily routine, and excessive use of TV, social media, or the internet, as well as obesity, reduced physical exercise, high caffeine and alcohol consumption, and smoking [139]. Shimura and colleagues assessed sleep hygiene and working environment across 6,342 employees from 29 companies and observed that job stressors, social support, commute time, regularity of dinner time, nightcap, frequency of vegetable intake, sunlight exposure in the morning in the bedroom, electronic visual display use at night, and frequent caffeine intake at night were independently associated with sleep disturbance [140]. Similarly, prolonged exposure to these conditions can lead to cognitive decline and accelerated brain aging over time [112, 113]. Another critical aspect related to altered sleep patterns and incidents of AD is chronic

social stress related to sex and race/ethnic discrimination [141, 142], which is often overlooked in clinical screening and management.

Collectively, the existing evidence indicates that genetic, environmental, social, and lifestyle factors interact to shape both sleep health and AD risk, offering multiple avenues for preventive interventions. However, further large-scale longitudinal investigations are necessary to understand the precise roles of each exposome factor and their interactions in the interplay between poor sleep and cognitive decline. This will be critical for developing successful individualized, public health, and policy-based approaches to reduce AD burden.

Circadian disruption

The circadian rhythm, synchronized by the suprachiasmatic nucleus (SCN), is an endogenous oscillation that aligns an organism's internal biological processes and sleep–wake behavior with the surrounding 24-h environmental cycle, in response to light stimulation [143]. Circadian disruption is not only a consequence of AD but also a prodromal symptom that precedes the onset of AD and drives its progression [42, 144]. Circadian dysrhythmia caused by SCN disruption was suggested to predispose neurodegeneration through multiple pathways, including circadian clock gene desynchronization [16, 145]. Circadian genes' alterations due to aging include phase shifts, rhythmicity alteration (both loss and gain), amplitude reduction, and expression disruption [146]. However, dysrhythmic pineal clock gene oscillation and melatonin secretion were found to be unique to AD and present even in the preclinical stage compared to normal aging [147]. AD-related alterations in the molecular clock may contribute to poor sleep and cognitive impairment [146]. A triple transgenic mouse model observed mild AD was associated with a disruption in the temporal patterns and quantitative levels of BMAL1, CLOCK, and CRY2 gene expression in the SCN [148]. Expression of *Chi3l1* gene, which regulates astrocytic protein YKL-40 and glial activation, is controlled by BMAL1, CLOCK, and PER1 & 2, and manipulating these clock genes impacted YKL-40 expression and A β plaque deposition, indicating that the circadian clock regulates AD-related

neuroinflammatory processes [149]. The hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei, together with the SCN, undergo changes with brain aging and are implicated in the pathophysiology of AD [150, 151]. Given their small size and deep midline location, however, conventional clinical MRI sequences have limited spatial resolution for reliably delineating these subregions in humans.

The physiologic patterns of CSF A β are dynamic and under circadian control, and aging, together with amyloid deposition, disrupt the CSF A β diurnal pattern and reduce its dynamics, respectively [152]. Interestingly, A β diurnal concentration is linked to sleep duration. Specifically, it decreases with accumulated sleep time and increases with prolonged wakefulness. However, no significant association has been found with various daytime activities [152]. Chronic sleep deprivation also leads to abnormal expression of clock genes in the mouse brain, abnormal tau phosphorylation in the retrosplenial cortex, and memory impairment [153]. In addition, circadian dysrhythmia in AD patients may result from decreased peptides, such as vasopressin produced in the supraoptic and paraventricular nuclei and neurotensin produced in the paraventricular nucleus, as well as an increase in the astrocyte/neuron ratio in the SCN [145, 154]. This phenomenon is more pronounced in the advanced stages of AD relative to normal aging [155], accompanied by a diminished number of melatonin-expressing neurons [156]. Fragmented sleep–wake rhythms due to circadian dysrhythmia are accompanied by more frequent daytime naps [157], disrupted SWS at night, and lower cognitive performance [158]. Chronic dawn-dusk simulations over several weeks reduced sleep–wake rhythm fragmentation and increased mood and alertness upon awakening and the strength of external *zeitgebers* in patients with dementia [159]. Hence, Circadian disruption interacts with AD pathophysiology, suggesting a bidirectional relationship. Abnormal expression and an interrupted rhythm of circadian clock genes, as well as neuron loss and an imbalanced astrocyte/neuron ratio in the SCN, are all involved in the pathogenesis of circadian dysrhythmia in AD. The complex interplay between circadian disruption and A β /tau accumulation along the trajectory of AD should be explored in future studies.

Orexin hyperexcitability

Orexin is a neurotransmitter that plays a crucial role in maintaining and stabilizing wakefulness by inhibiting sleep-promoting neurons [160] and modulating the paraventricular nucleus that controls sleep–wake cycles [161, 162]. Orexin secretion depends on the SCN activity, thus exhibiting a 24-h circadian rhythm [163]. As a neuromodulator of sleep and wakefulness, orexin is deeply involved in the pathogenesis of circadian dysrhythmia in AD [164]. In aged mice, the hyperexcitability of arousal-promoting orexin neurons is linked to fragmented sleep, which is related to the functional impairment of KCNQ2/3 channel-mediated M-current and the anatomical loss of KCNQ2 in these neurons, leading to a reduced threshold for the sleep-to-wake transition [41]. In humans, Orexin dysregulation has been reported in both AD and mild cognitive impairment (MCI) patients, and it was negatively associated with total sleep duration in AD and sleep efficiency in MCI, but positively linked to insomnia severity index in both groups [165, 166]. Furthermore, a higher CSF orexin level was associated with REM sleep disruption and sleep fragmentation in MCI [167]. Hence, upregulation of orexin seemed to align with the characteristic sleep disruptions in AD, indicating its involvement along the AD trajectory, particularly at the early stage. Genetic modulation of orexin has a robust impact on sleep regulation, which in turn modulates A β pathology in the brain. Specifically, sleep deprivation increases the amount of A β pathology in the brain, whereas a 12% increase in sleep time is linked to >50% decrease in A β accumulation [168]. It is important to note that when these orexin knockout mice were sleep-deprived, they still accumulated A β plaques. Thus, it was the sleep time, not the absence of orexin expression per se, that impacted A β plaque deposition in these mice. It has been shown that the administration of orexin agonists or sleep deprivation leads to a higher rate of A β accumulation in brain interstitial fluid, while the infusion of a dual orexin receptor antagonist reduces A β plaque formation [20]. A similar phenomenon was also observed in humans, where A β concentration and tau phosphorylation decreased after administration of dual orexin receptor antagonists [32]. Orexin may exacerbate memory impairment and synaptic plasticity deficits in the hippocampus by disrupting circadian rhythms,

thereby increasing A β production and decreasing its clearance [169]. Recently, it has been shown that orexin receptor antagonist (i.e., Lemborexant) and genetic ablation of orexin receptor 2 can improve tau-associated impairments in mouse models [170] (*see Sect. "Novel treatment opportunities for personalized medicine" for details*). Thus, orexin excitability may disrupt the sleep–wake cycle and, therefore, lead to A β and tau accumulation in the brain. However, a meta-analysis highlights that orexin levels may vary at different stages of AD [171]. The underlying neurobiological mechanism of orexin and its interaction with circadian dysrhythmia in the pathophysiology of AD should be further explored, particularly in human studies.

Sleep and AD pathophysiology

Numerous studies have proposed models of how sleep disturbances can affect the balance between the production, clearance, and accumulation of core pathological proteins and neurodegeneration in AD. This section will explore the link between sleep and biomarker proliferation using the AT(N) (amyloid, tau, neurodegeneration) framework [172] supported by recent biofluid and neuroimaging evidence [173], examining its effects on brain regions critically affected in AD pathophysiology (Fig. 2).

Amyloid (A) Evidence suggests a strong cross-sectional and longitudinal relationship between A β deposition and sleep disturbances. Indeed, various studies indicate that sleep deprivation, suppression of SWS, deficits in SWA, and multiple sleep disorders are linked with both acute and long-term brain structure and function abnormalities [183] and increases in A β burden [184–186]. Disruption of SWS and REM sleep can elevate plasma A β levels and decrease gray matter in the posterior cingulate cortex in individuals with MCI, respectively [187]. Acute sleep deprivation, particularly affecting SWS, and poor sleep quality can increase CSF A β levels even in healthy adults via more production or less brain clearance [184, 188, 189]. Positron emission tomography (PET) scans indicate that severe sleep disturbances are linked to increased A β deposition. Inadequate and disturbed sleep correlates with a higher global burden and increased A β depositions in AD-associated

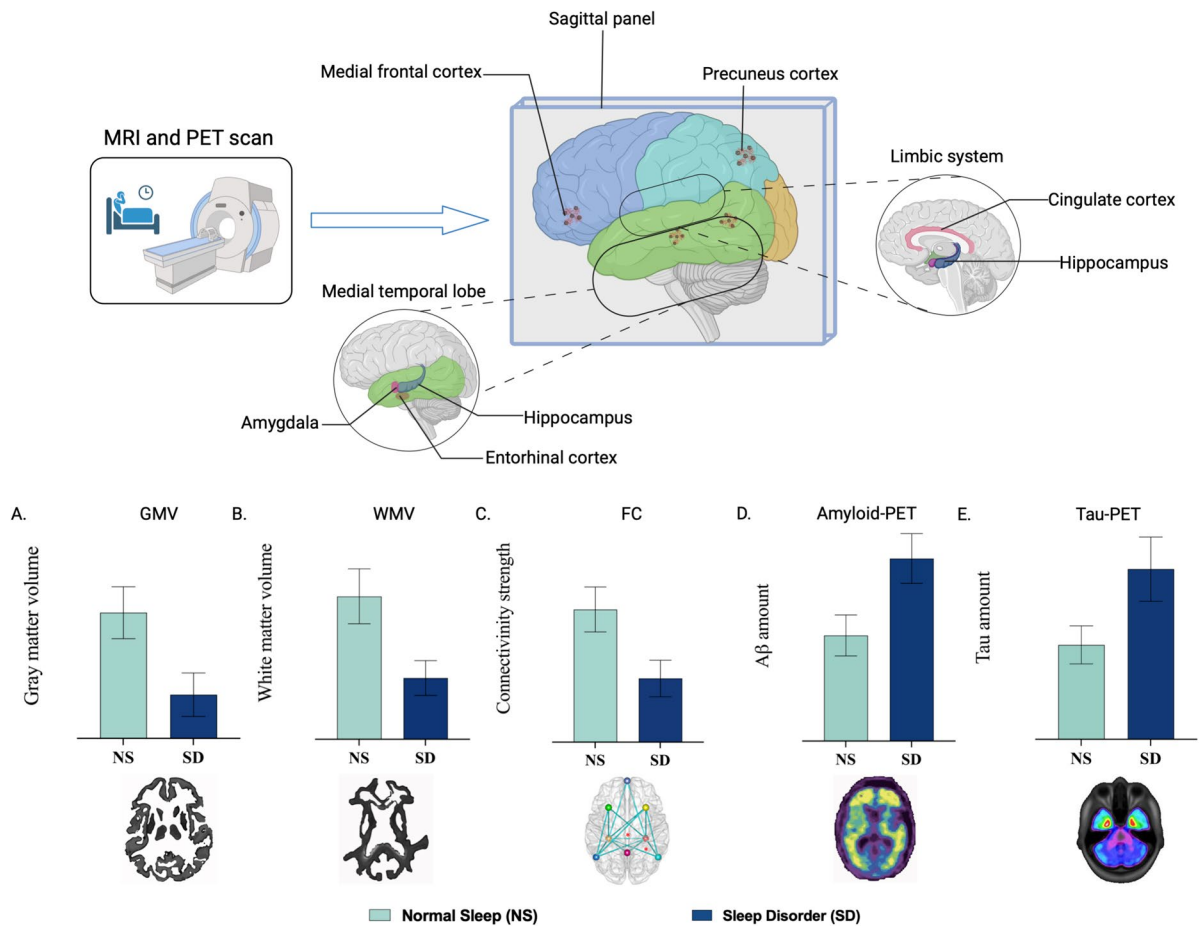


Fig. 2 Conceptual illustration of neuroimaging evidence on the sleep-AD interrelationship. **A:** gray matter volume reduction in the medial prefrontal cortex, precuneus, hippocampus, amygdala, and entorhinal cortex [57, 174, 175]. **B:** total white matter volume reduction [176]; **C:** Diminished functional connectivity in the default mode network [177, 178]; **D:** Increased

amyloid beta deposition in the medial prefrontal cortex, precuneus, and cingulate cortex [179–181]; **E:** Increased tau deposition in the medial temporal lobe, entorhinal cortex, and hippocampus [182]. Bar plots reflect schematic increases or decreases of neuroimaging markers. We created this figure in Biorender.com ([https:// BioRender.com/5n4k4vg](https://BioRender.com/5n4k4vg))

regions, including the angular gyrus, cingulate gyrus, precuneus, and medial frontal cortex [179, 190, 191] (Fig. 2). These findings are prominent in patients with OSA, who exhibit greater brain A β levels cross-sectionally, particularly in the posterior cingulate gyrus and temporal cortex, and more longitudinal increases in PET-measured A β and CSF-measured tau levels [192–194]. Patients with SDB exhibit greater A β accumulation, increased GM volume, perfusion, and metabolism in AD-sensitive brain regions, including the precuneus and posterior cingulate cortex [180, 195], which may be because the participants were at an early stage with milder severity and few

symptoms, and in this stage, the brain still has high cognitive reserve [196]. This association between OSA and A β pathology may be driven by the impact of OSA on SWA. Longitudinal findings revealed that in OSA patients, increases in slow oscillation power and decreases in delta power are associated with greater longitudinal A β burden [197]. Finally, a robust association between self-reported SDB and A β pathology, but not glucose metabolism or gray matter volume (GMV), was observed in the PET images and CSF of patients with AD [181]. The link between OSA and AD could be the result of age-related cerebrovascular susceptibility [198, 199]. Collectively,

these findings show that A β accumulation may be preferentially associated with sleep loss, poor sleep quality, SWS disruption, and the presence of OSA.

The mechanisms driving this effect are currently unclear, though there are three, non-mutually exclusive candidate pathways that could result in the observed disruptions in the balance of A β production and clearance [14, 200]. First, sleep disturbances may result in increased wake-like activity during sleep, which in turn increases neurometabolic activity and consequently A β production. This is supported by evidence that acute suppression of SWA increases CSF A β proteins selectively, without impacting overall protein levels or proteins associated with glial cells [184]. Further support of this comes from rodent studies showing that chronic sleep restriction increases markers of oxidative stress, which is related to elevated β -site APP-cleaving enzyme 1 (BACE1) expression, resulting in increased A β production [201]. Second, sleep disturbances may disrupt glymphatic clearance of A β , a possibility supported by evidence that A β clearance rate is increased during NREM sleep [43]. Third, sleep disturbances may disrupt the phagocytosis and degradation of A β by microglia. This last possibility is supported by evidence showing that enhancing SWA during NREM sleep increases markers of microglial activation and migration to A β plaques, alongside reducing A β plaque burden [202]. Disruption of any combination of these processes would likely shift the balance between A β production and clearance, leading to increased A β accumulation and thus AD pathophysiological progression.

Tau (T) The relationship between sleep and tau pathology mirrors the findings regarding A β . Seminal rodent studies demonstrated that sleep deprivation and SWA attenuation increase tau burden, hyperphosphorylation, and spread, as well as neurofibrillary tangle (NFT) burden [19, 20, 203]. In humans, CSF tau levels increased by more than 50% following sleep deprivation [19]. Chronic sleep deprivation may also significantly enhance tau propagation, with evidence suggesting that poor sleep quality at home before sleep deprivation is strongly associated with increased CSF tau levels [184]. Diminished NREM SWA similarly appears to exacerbate tau pathology, as evidenced by elevated tau-PET signal, and factors

such as race, ApoE4 genotype, and use of sleep medications may further influence this [204–206]. RBD exhibits greater tau accumulation in AD-sensitive areas, such as the locus coeruleus, and symptom severity is positively associated with tau accumulation in this region [207]. Moreover, poor sleep quality has been linked to higher tau burden in regions corresponding to Braak Stages III & IV, but primarily among individuals with elevated cerebral A β [208]. Other findings also found a positive association between sleep duration and tau accumulation, especially in the amygdala and hippocampus, independent of A β load [209].

Several studies in both rodents and humans have demonstrated that AD-related pathophysiology alters on macro- and micro-sleep architecture [14, 210]. Animal models of A β and tauopathy consistently show fragmented sleep architecture, along with disruptions in SWS and sleep spindle expression [211–213]. In humans, NREM sleep alteration, characterized by a higher percentage of N1 sleep and a lower percentage of SWA, was associated with increased tau accumulation and lower cortical thickness in temporal regions, particularly the entorhinal cortex and inferior temporal cortex [205]. Across tauopathies, tau deposition in various sleep and wake-promoting nuclei is associated with fragmented sleep–wake brain states [214]. Interestingly, even in older adults without MCI or AD, A β and tau pathology are related to deficits in SWA, theta-band activity, and SWS-spindle coupling [182, 186, 206, 215–217]. In rodent tauopathy models, tau accumulation in the medial temporal lobe is also associated with reduced hippocampal ripple expression, a marker of degeneration of hippocampal GABAergic interneurons [218]. Importantly, in many of these studies, the effects of A β and tau pathology on sleep expression were also associated with corresponding impairment in sleep-dependent memory performance, indicating that the effects of A β and tau pathology on sleep contributed to the cognitive decline associated with AD pathophysiology [14, 186, 202, 217].

Neurodegeneration (N) and brain reorganization Neurodegeneration, the third component of the AT(N) framework, is also exacerbated by sleep disturbances. Neuroimaging meta-analyses in OSA and insomnia disorder identified consistent GMV

reduction and dysfunctions in regions such as the hippocampus, amygdala, central insula, and anterior cingulate cortex, all of which coordinate cognitive, emotional, and executive functions [183, 219, 220], are sensitive to age-related changes [15], and are implicated in AD pathology [221]. Microstructural integrity of the locus coeruleus, an AD pathology, Microstructural integrity of the locus coeruleus, a region involved in the pathology of AD, may modulate resilience to sleep deprivation [222]. A few studies demonstrated reduced glucose uptake in the hippocampus, amygdala, posterior parietal cortex, and cingulate cortex in patients with OSA, alongside volume reductions in the basal forebrain and hypothalamus [57, 181, 223, 224]. These alterations mirror patterns observed in early AD, highlighting overlapping neurodegenerative pathways. Disrupted sleep has also been linked to GMV alterations and decreased white matter diffusivity in the orbitofrontal cortex, middle temporal cortex, precuneus, posterior cingulate cortex, and thalamus [225, 226]. Additionally, time spent in SWS may correlate with cortical thickness in these regions [227].

Self-reported sleep disruptions and sleep/wake rhythm fragmentation are associated with medial temporal lobe atrophy, which is particularly significant given its vulnerability to tau pathology during pre-dementia stages of AD [204, 228, 229]. For instance, older individuals with excessive daytime sleepiness and fatigue showed substantial reductions in cortical thickness in temporal regions and accelerated brain aging [204]. White matter integrity across the brain has also been associated with steeper slow wave slopes and higher fast-frequency sleep spindle density [230, 231]. Longitudinal studies further illustrate these effects. A two-year follow-up study on cognitively normal participants revealed that poor sleepers exhibited greater volume loss rates in AD-related regions compared to normal sleepers [232]. Another six-year follow-up study identified that shorter nighttime sleep and longer daytime sleep were associated with more severe white-matter damage, with perivascular space burden mediating these effects [233]. Despite the central role of the thalamus in sleep, there is currently no human evidence linking age- or AD-related thalamic integrity and functional changes with spindle deficits. Rodent studies, however, have shown that aging impacts the thalamic

reticular nucleus structure and function [234–236]. In humans, sleep spindle deficits have instead been linked to hippocampal volume, white matter integrity, and fluid biomarkers of tau proteins and neurodegeneration [217, 230, 237].

Functional brain activity studies reveal that poor sleep is associated with alterations in large-scale brain networks, particularly the default mode network (DMN), salience network (SN), and frontoparietal network (FPN). Individuals with insomnia and SDB exhibit disrupted connectivity within these networks [177, 178, 238]. Neuroimaging evidence indicates that NREM sleep engages specific large-scale networks, including the DMN and FPN, which show altered connectivity both in sleep disorders and in aging [239]. Decreased connectivity in the DMN and FPN, as well as increased connectivity in the SN, was identified in AD patients, while the only impaired functional connectivity in MCI was the precuneus in the DMN [240], and the dysregulated networks were suggested to be associated with anosognosia in AD patients [241]. Meanwhile, insomnia symptoms demonstrate network-specific effects across the AD continuum, namely triple-network hypoconnectivity in AD, and hyperconnectivity in MCI and controls, which further correlate to significant cognitive decline and depressive symptoms [177]. Another study in AD patients with sleep disturbances observed diminished intrinsic brain activity in the left hemispheric regions associated with the sensorimotor and visual networks, indicating the impact of sleep disturbances on networks associated with AD progression [242]. Beyond network connectivity, dysregulation of the Hypothalamic–Pituitary–Adrenal axis and high cortisol levels can mediate the relationship between poorer cognitive function and loneliness, a common experience among individuals with AD [243]. Despite these associations, the accurate directionality and mechanistic relationship between sleep expression and cortical morphology or function remain unclear, as the cortex does not directly regulate sleep–wake transitions or maintain sleep stages. It is, instead, more likely that these findings more plausibly reflect relationships between the frontotemporal cortex and local expression of cortically regulated sleep oscillations that define NREM sleep stages.

In sum, emerging literature highlights a complex series of bidirectional interrelationships between sleep disturbance, A β and tau pathology, and

neurodegeneration. Consolidated NREM sleep and SWS facilitate active clearance of AD pathology and promote resilience in the face of increasing AD risk. In contrast, sleep disorders and NREM sleep disturbances promote active accumulation of AD pathologies, contributing to neurodegenerative processes that can trigger cognitive decline. These pathological changes can further erode the sleep mechanisms that commonly sustain cognitive performance and neural resilience, creating a self-reinforcing cycle that accelerates cognitive decline.

Waste clearance via the glymphatic system

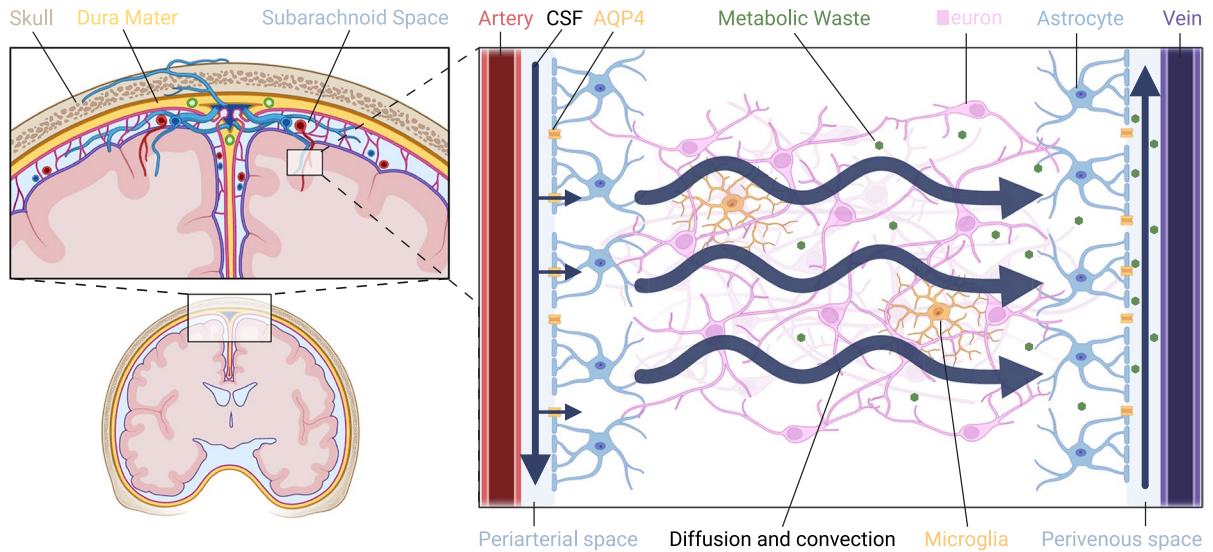
Recent advancements in the field of waste protein clearance indicate that impaired clearance is not simply a consequence of the propagation of large, insoluble plaques and fibrils [244, 245]; rather, impairments in waste protein clearance may be present before clinically significant pathological burden is apparent [245]. Prior to the discovery/introduction of the brain's glymphatic system, clearance of waste proteins from the central nervous system was thought to be solely driven by autophagy, ubiquitination, and phagocytosis by activated microglia [202, 246]. Due to the presence of the blood–brain barrier and the absence of a lymphatic system within the brain itself, the dominant theory was that the CNS recycled most of its waste protein substrates [247, 248]. The discovery of a cerebral fluid transport system dependent on astroglial water transport, analogous to the peripheral lymphatic system [244], challenged this view. This so-called “glymphatic” (glia-lymphatic) system is defined by four sequential processes. First, CSF is driven into the brain's perivascular spaces (PVS) by arterial pulsation. Second, AQP4 water channels on astroglial endfeet mediate CSF passage into the parenchyma, where it combines with interstitial fluid (ISF). Third, the CSF/ISF commixture diffuses or convects through the parenchyma, delivering nutrients and removing waste to the perivenous space. Fourth, the CSF/ISF commixture is drained into cranial egress sites, including the perineural sheaths of the cranial and spinal nerves, the dural sinuses, and the arachnoid granulations [44, 249] (Fig. 3). Among its other hypothesized functions, the glymphatic system is considered an important protective mechanism against waste protein aggregation [244]; a finding that

has since been replicated in animal and human studies [43, 248, 250–253].

Another observation made in parallel with the discovery of the glymphatic system was its remarkable dependence on NREM sleep [43, 254], with both CSF influx and glymphatic clearance being enhanced during NREM sleep and anesthesia [43]. NREM-contingent norepinephrine oscillations appear to play a crucial role in regulating glymphatic flow [46]. A new study found that both optogenetic stimulation of the locus coeruleus and Zolpidem-induced suppression of norepinephrine oscillations resulted in a marked reduction in glymphatic flow [46]. Another key driver of glymphatic function is cranial arterial pulsation, an artifact of respiration and cardiac activity, which are both affected by circadian rhythms [255]. Studies using CSF tracers showed a nearly 20-fold increase in influx at sleep onset [43]. Interstitial spaces generally expand during sleep, which is conducive to parenchymal flow [43, 256]. Sleep deprivation appears to significantly reduce glymphatic clearance, while recovery sleep restores it [257]. However, this growing body of evidence is not without contention [48]. A recent photometry study found that brain clearance (or rather, parenchymal diffusion) was reduced during sleep and anesthesia [47], though a multimodal replication study did not corroborate their findings [258]. Additional rigorous imaging techniques will be required to fully disentangle the complex relationship between NREM sleep, circadian rhythm, and glymphatic function in humans. For example, Hirschler and colleagues recently introduced a non-invasive MRI method to measure CSF mobility in humans [259], which offers hope for addressing questions about glymphatic clearance in AD.

It has been suggested that glymphatic dysfunction may be the final common pathway in the relationship between sleep disturbances and AD pathogenesis [17]. One landmark study found that a single night of sleep deprivation following intrathecal injection impaired clearance of the contrast agent (i.e., gadobutrol) from brain regions known to deposit A β plaques or neurofibrillary tangles in early stages of AD, including the prefrontal cortex, anterior and posterior cingulate cortex, precuneus, and the amygdala [248]. The elevated tracer level was still detectable after 48 h of sleep, highlighting the long-lasting effect of sleep deprivation on glymphatic system dysfunction [248]. Siow and colleagues also found a link

A. Cognitively Normal



B. Alzheimer's Disease

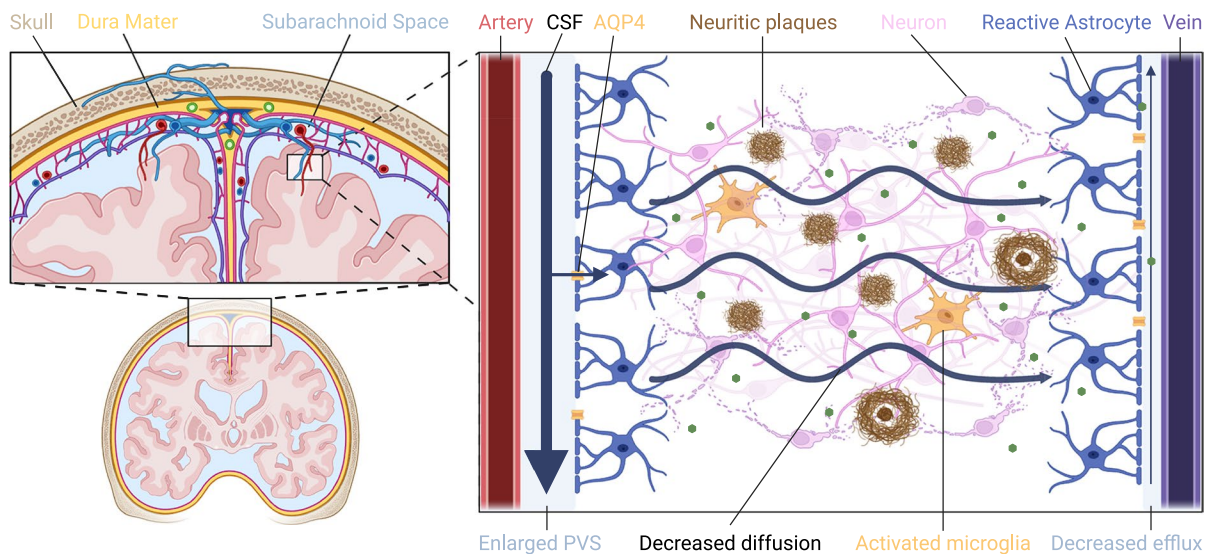


Fig. 3 A schematic representation of glymphatic clearance in (A) cognitively normal individuals and (B) Alzheimer's disease. Glymphatic impairments, characterized by AQP4 downregulation, enlargement, and decreased CSF diffusion

and efflux, result in the accumulation of metabolic waste and the formation of neuritic plaques. This figure was created in Biorender.com (<https://BioRender.com/z17o561>)

between reduced sleep duration and more severe sleep apnea, cognitive impairment, GMV abnormalities, and a lower diffusion along the perivascular space (DTI-ALPS) index, which has been initially proposed as an MRI-based marker of glymphatic efflux [260, 261]. Although recent findings questioned the

validity of DTI-ALPS as valid measure of glymphatic clearance (REF: PMID 41631990). In other studies, a lower DTI-ALPS index predicted GMV atrophy, accelerated A β burden, clinical progression, and cognitive decline in AD [262]. The DTI-ALPS index represents an early attempt to image the glymphatic

system non-invasively; other non- or minimally invasive approaches include diffusion kurtosis imaging sequences to calculate the ALPS index (DKI-ALPS) [263], PVS volumetry, free water mapping in the white matter, BOLD-CSF coupling, ultrafast fMRI, arterial spin labeling, and multimodal PET/MRI [49, 264–267]. The degree to which structural alterations in the white matter due to ageing or neurodegeneration contribute to the observed effects across indices remains uncertain, though specific indices, such as DKI-ALPS, aim to account for this potential confound through non-Gaussian approaches [261]. Recent studies have also highlighted PVS alterations in OSA [268, 269]. A more significant limitation is that none of these indices directly assesses solute exchange, severely limiting their interpretability [49]. Thus, despite interesting trends across the AD continuum, these indices cannot yet be considered definitive indicators of glymphatic function without further validation.

Glymphatic failure, which has been shown to expedite clinical manifestations, may also occur as a result of genetic variation. SNPs affecting the structure, expression, and localization of AQP4 near the astroglial endfeet may significantly inhibit the transport of CSF into the parenchyma [270], leading to increased amyloid burden [271]. Genetic deletion of AQP4 in mice has been associated with an acute reduction in glymphatic exchange and an increase in A β burden [272, 273]. Another mouse tauopathy study found a decrease in CSF-ISF exchange accompanied by AQP4 depolarization and tau accumulation [274]. One intriguing theory suggests that even the unusual, prion-like spread of A β [275] may be due to glymphatic failure resulting from AQP4 deletions [276]. In essence, it proposes that attenuated glymphatic flow fails to clear the protein aggregates, instead facilitating their diffusion throughout the interstitium. Interestingly, this theory seems to be supported by both the spatial pattern of A β spread [17, 262] and the effects of age and AD on AQP4 expression and glymphatic clearance [273, 277]. While the glymphatic system provides a compelling link between sleep disturbances and AD pathogenesis, it is essential to note that other waste clearance mechanisms remain vital for mitigating AD risk. The following section will discuss the inflammatory control of waste proteins by microglia and astrocytes, one of the other key protection mechanisms against AD pathology. Additionally,

other studies have found evidence of alternative clearance pathways, including the intramural periaxonal drainage system and the meningeal lymphatic system, both of which contribute significantly to the removal of waste proteins from the CNS [278, 279].

Neuroinflammation

In Dr. Alois Alzheimer's initial histopathological examination of AD, morphological changes in microglia were noted as a key pathological observation [280]. Since this initial finding, a growing literature has identified neuroinflammation as a core biological feature driving AD pathophysiology [281], with changes in microglia and astrocyte function playing a central role [282, 283]. Contemporary theories primarily focus on the role of CNS inflammation in facilitating the accumulation of tau pathology, neurodegeneration, and cognitive decline downstream A β pathological accumulation [284], potentially due to the impact of A β on neuronal hyperexcitability [52, 285]. Inflammatory responses in the CNS, including the orchestrated actions of immune, vascular, glial, and neuronal cells, can be triggered by increased neuronal activity [286]. Under normal conditions, neurogenic inflammation may play a crucial role in maintaining synaptic homeostasis during periods of increased metabolic demand [286]. For instance, multidirectional synapse cross-talks between astrocytes, neurons, glia, and vascular smooth cells have all been shown to act as potent regulators of neuronal spiking, synaptic plasticity, and cerebral blood flow, all of which likely modulate the computational power and plasticity within neural networks [287]. However, microglia and astrocytes have been shown to release cytokines, interleukins, nitric oxide, and other potentially cytotoxic molecules after exposure to A β , thereby exacerbating the neuroinflammatory response [288]. Neuroinflammation can also be an initial driver of AD pathophysiology, preceding A β plaque deposition [289]. Indeed, the emergence of chronic, low-grade inflammation in older adults in the absence of an infection, termed “inflammaging”, is thought to contribute to the development of neurological illnesses, including AD [91]. Emerging findings indicate that sleep disturbances are associated with both neuronal excitability and inflammation, suggesting

that sleep may influence AD risk through its interactions with the immune system.

While the relationships between sleep and inflammation are complex [290], chronic sleep disturbances consistently lead to a proinflammatory response. For example, a large-scale meta-analysis across 72 studies found that sleep disturbances and both short and long sleep durations are associated with higher levels of systemic C-reactive protein (CRP) and interleukin-6 (IL-6) [101]. Studies also show that shorter sleep duration, disrupted sleep architecture, and the presence of hypoxemia during sleep are all associated with increased IL-6, CRP, tumor necrosis factor alpha (TNF- α), and interferon gamma (INF- γ) in older adults and AD caregivers [291–293]. In addition to markers of peripheral inflammation, markers of CNS inflammation are also elevated in association with sleep disturbance. Glial fibrillary acidic protein is a marker of astrocyte activation and is elevated in the plasma of middle-aged OSA patients compared to controls, with the degree of elevation associated with the severity of hypoxemia [294]. Local deficits in sleep spindle expression in older, A β -adults were also associated with multiple CSF markers of astrocyte and microglial activation, and these sleep deficits predicted impaired sleep-dependent memory consolidation [50].

The relationship between chronic sleep loss, metabolic disorder, chronic inflammation, and AD pathophysiology may be driven by neuroinflammation mechanisms [295], which affect brain's glymphatic function [45]. Data from *Drosophila* demonstrate that A β -induced neuronal hyperexcitability is magnified by sleep deprivation [296]. It is therefore possible that this results in an exaggerated inflammatory response. The locus coeruleus, a brainstem nucleus that promotes arousal and cognitive functioning, is quiescent during sleep, supporting metabolite clearance through the noradrenergic pathway [46, 297]. In addition to its role as a neurotransmitter, NA has potent anti-inflammatory, anti-oxidative, neurotrophic, and neuroprotective actions [288], and locus coeruleus-noradrenergic release has been postulated as a potent central regulator of spatiotemporal neural activation and energy expenditure [298]. The number of cells in the locus coeruleus and the concentration of noradrenergic in the brain decrease during normal aging, a process that is accelerated in AD [288]. Thus, early degeneration of the locus coeruleus and

subsequent loss of noradrenergic-mediated innervation could substantially promote the inflammatory response to any stimulus, including A β . Experimental loss of noradrenergic has been shown to compromise microglial migration and A β phagocytosis in vivo, suggesting that a loss of noradrenergic tone increases inflammation and A β deposition [288]. In contrast, higher sleep quality mitigates the effects of mutations in the adenosine triphosphate binding cassette subfamily A member 7 (ABCA7) gene on cognitive function in older African Americans, a gene associated with microglial homeostasis [119, 299]. Furthermore, an optogenetic study in rodents demonstrated that increasing SWA reduced A β plaque burden, likely by facilitating microglia-dependent phagocytosis [202]. In sum, these data indicate that chronic poor sleep increases inflammation and may amplify the inflammatory response to A β pathology, whereas higher sleep quality may counteract these effects and promote the clearance of A β pathology.

In addition to interactions with A β , microglial dysfunction contributes to the spread of tau pathology through synaptic and non-synaptic transmission, including exocytosis of microvesicles, such as exosomes [300]. Sleep problems increase the accumulation of endosomes and lysosomes and promote increased autophagy in initial disease stages [301]. However, in later stages, sleep disturbances disrupt autophagy activation in the hippocampus [302], likely due to corticotropin-releasing hormone activation resulting from chronic sleep disturbances [283]. These findings indicate that sleep disturbances may also directly impact the effects of inflammation on tau pathological spread. Indeed, a seminal study demonstrated that chronic sleep restriction facilitates the spread of tau pathology from the hippocampus to the locus coeruleus [19], supporting this possibility.

Collectively, chronic sleep disturbances contribute to neuroinflammation, in part by influencing neuronal hyperexcitability, which facilitates AD pathophysiology [51]. Neuroinflammation has already been perceived as one of the principal treatment targets in people with AD [288], and in some sleep disorders, such as OSA [303, 304]. For example, there is evidence that OSA induces increases in oxygen free radicals and decreases antioxidant capacity, effects that are reversed by one year of adherent CPAP therapy [305]. However, from a clinical perspective, due to the complexity of the immune system, any

modulation of inflammatory signaling pathways may result in unpredictable consequences [286], and thus, intervention development focused on inflammatory targets must proceed with caution.

Leveraging machine learning for precision medicine

Despite ongoing investigations, it remains unclear how novel findings across physiological, neuroimaging, and behavioral modalities can be integrated to better understand the relationships between sleep and AD at the individual patient level. As discussed, the existing evidence indicates that chronic sleep disturbances increase the risk for AD dementia. This means that while experimental sleep deprivation protocols can advance our understanding of transient causal interactions between sleep and AD-related factors, other approaches are needed to gain insight into how chronic sleep disorders interact with the trajectory of AD pathophysiology. Identifying risk factors and general trends in the population thus requires an epidemiological perspective, which necessitates large datasets that encompass sleep and circadian patterns across the population's variability. Such resources are now available in initiatives such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and UKB [306], where sociodemographic, lifestyle, environmental, and biomedical variables have been collected in middle-aged and older participants.

Clinical and population cohorts offer the opportunity to study the association between sleep and AD within a multifactorial context. As outlined in Sect. "Exposome factors", a range of interrelated exposome factors is assumed to interact with sleep and cognitive phenotypes and with dementia risk, forming a complex, multifactorial context. By employing multivariate methods, such as Canonical Correlation Analysis, and artificial intelligence approaches, including advanced machine learning and deep learning, we can capture the complex patterns among a range of exposome factors, phenotypes, sleep health, neuroimaging, and cognitive performance. Future large-scale, data-driven studies will contribute to understanding how the individual profile of sleep health and AD risk is embedded into broader biomedical and exposome profiles in the population.

Another important consideration in the study of sleep-AD interaction, particularly in associations with other phenotypical aspects, is the individual variability among patients, not only at the symptomatic level, but also at the pathophysiological level. For example, it is now widely acknowledged that different subtypes of brain atrophy, brain metabolism, and cognitive impairment patterns exist among AD patients [307, 308]. Different subtypes based on tau deposition have been hypothesized [309, 310]. Given this variability, it is reasonable to assume that individual pathophysiological and symptomatic profiles of AD patients are also related to the profile of sleep-exposome factors. From a personalized medicine perspective, this raises a critical challenge for making predictions regarding diagnosis and prognosis at the individual level. Predictive or supervised machine learning approaches are indispensable in addressing this challenge [66, 311]. These models enable the prediction of individual phenotypes, such as cognitive status or disease diagnosis, based on the patient's profile across a wide range of measurements, including subjective and objective sleep profiles, circadian rhythm patterns, and brain function, metabolism, and morphology. Although these models will primarily contribute to the disentangling of multivariate patterns in the complex context of interaction between sleep and dementia, there is hope that they will ultimately be applied to individual prognosis in clinical settings. In the meantime, these computational approaches can be refined by capitalizing on large-scale genetic/phenotypic/neuroimaging databases, as well as international data collection initiatives such as the ENIGMA-Sleep consortium [312, 313]. A notable caveat of these databases is that sleep measurements are often relatively coarse, with sleep quality assessment generally based on self-reporting, frequently using non-standardized questionnaires, and varying across sites. To address this limitation, future large-scale data collection efforts should prioritize more harmonized, detailed sleep phenotyping, including the collection of ambulatory objective data.

Novel treatment opportunities for personalized medicine

Existing neurobiological insights support the hypothesis that sleep is a modifiable treatment target for

AD progression during its prodromal phases [34]. These insights have not gone unnoticed in biomedical research, and various therapeutic approaches have already been suggested that may increase sleep quantity and quality, defer the accumulation of tau and A β , and protect against cognitive decline [14, 170, 314, 315]. Here, we outlined a few noteworthy approaches, discuss their benefits and limitations, and explain how they improve sleep patterns and theoretically delay AD progression.

It is well established that social contact and lifestyle optimization, which encompasses increasing physical activity, managing obesity, enhancing cardiovascular and metabolic health, reducing alcohol and tobacco consumption, and addressing neuropsychiatric comorbidities as early as possible, is beneficial for both sleep quality and brain health [139, 316–318]. Lifestyle choices, particularly those related to exercise, diet, alcohol intake, omega-3 consumption, and chronic stress, may also affect glymphatic function [319, 320]. This further connects the notion that maladaptive lifestyle behavior can modulate both the neuroprotective effects of sleep and the severity of cognitive decline in AD. Multidomain interventions, exemplified by the Multidomain Alzheimer's Prevention Trial (MAPT) and the Body Brain Life program, involve long-term, in-person or online counseling on various topics, including exercise, nutrition, drug intake, mental health, and social/cognitive engagement, which are essential first steps to AD prevention [321, 322]. However, some of these trials did not include sleep management, which may have limited their efficacy in this context.

Insomnia disorder is characterized by disproportionately negative perspectives on sleep continuity and quality and is often treated using cognitive-behavioral therapy for Insomnia (CBT-I), which focuses on the restructuring of thoughts, feelings, and behaviors [323]. CBT-I applies methods such as time-in-bed restriction, stimulus control, relaxation exercises, and changing beliefs to alter a negative attitude toward sleep. Comprehensive reviews of CBT-I outline its efficacy in improving sleep initiation and maintenance [324, 325]. Clinical trials of CBT-I in AD patients with insomnia showed promising results [326, 327]. For patients with OSA, CPAP is the first-line treatment, though it is limited by costs, adherence, and availability [328, 329]. When CPAP is ineffective, bariatric surgery may also be considered. In

addition to improving sleep quality and oxygenation, CPAP therapy enhances vascular function, including improvements in endothelial reactivity and reductions in arterial stiffness and blood pressure, which may contribute to its broader cardiovascular and neuroprotective effects [330, 331]. Treating OSA with CPAP can lead to better cognitive outcomes for AD patients [332]. In a few studies [33, 333], CPAP use in patients with OSA improved CSF markers of A β and tau, providing proof-of-concept evidence that treating sleep disorders may affect AD risk. This is further supported by limited epidemiological data, showing that CPAP treatment may delay the age of MCI and AD onset by up to a decade in patients with SDB [334]. While larger studies are clearly needed, these findings provide evidence that targeting the underlying cause of sleep disturbances may impact AD biomarkers and the time course of AD expression in a clinically relevant manner.

Sleep fragmentation and disruption of sleep architecture are common facets of aging, amplified by AD pathophysiology [15]. Total sleep time, sleep latency, time spent in wakefulness, and NREM sleep are factors that are affected by aging [15]. The sleep architecture of AD patients shows similar, yet exacerbated, disruptions compared to their elderly peers, except for profound deficits in REM sleep expression, which is also observed in other degenerative diseases [335]. In particular, SWS, which may benefit memory consolidation and glymphatic function, is markedly attenuated in AD [14, 17, 39]. AD patients may also specifically benefit from SWS-enhancing treatments, including non-invasive, long-term auditory and transcranial stimulation, and SWA-stimulating drugs such as tiagabine and gaboxadol [336], though large phase III clinical trials targeting AD biomarkers will need to be conducted to confirm this possibility. Nevertheless, some studies reported increased glymphatic clearance following SWS-enhancing therapy [202, 337].

Circadian dysrhythmia, i.e., the gradual loss of the joint timekeeping capacity of neural cells, is another target for therapeutics aimed at improving sleep quality in AD patients [16, 42]. Alongside lifestyle improvements, including increased daytime light exposure, circadian dysfunction is best mitigated through chronotherapeutic protocols, which typically involve intervening at distinct time points along the patient's day-night cycle [338]. These interventions may include basic light therapy, gamma

(40 Hz) frequency light therapy, and administration of drugs targeting cortical, limbic, or SCN populations involved in time-keeping and the generation of circadian oscillations [144]. Melatonin supplementation has also been found to be effective in preventing “sundowning,” which refers to a state of restlessness and confusion that occurs from late afternoon into late evening in AD patients [339]. A recent animal study demonstrated that multisensory stimulation enhanced glymphatic clearance of A β [252]. Similarly, acoustic enhancement of sleep slow oscillations can improve sleep-dependent memory storage in older adults [340]. Moreover, dual orexin receptor antagonists (DORAs), including suvorexant, lemborexant, and daridorexant, not only improve sleep quality but also reduce tauopathy and hippocampal-dependent spatial memory, particularly in male mice [170, 341]. However, since these treatments are relatively novel, further clinical evaluation in humans is necessary before they can be widely implemented.

In sum, a growing body of evidence has shown that improving sleep health benefits the cognitive well-being of patients and actively suppresses AD-related pathophysiological progression. The optimization of lifestyle choices, expedited treatment of (sleep-related) comorbidities, and enhancement of SWS activity and circadian rhythm directly affect the efficacy of key neuroprotective mechanisms. Why, then, does a large-scale application of these interventions remain challenging? Indeed, although sleep disturbances are inexorably linked to AD progression, the forms, causes, and substrate of these disturbances are often highly variable.

Conclusion

This review provides a comprehensive conceptual framework linking poor sleep and AD through exposome factors and underlying neurobiological mechanisms, integrating recent findings from both animal and human studies. This framework supports a hypothetical model whereby genetic and exposome factors interact with brain aging to facilitate inflammaging and metabolic dysregulation, leading to sleep and circadian disruptions that accelerate AD pathological accumulation through increased A β and tau production and glymphatic

failure. AD pathophysiology further disrupts sleep, creating a vicious cycle promoting neurodegeneration, cognitive decline, and, ultimately, conversion to dementia. We emphasize the significance of inter-individual variability, a key element of precision medicine, in addressing the shared burden of sleep disturbances and AD. We further advocate for the aggregation of multifactorial phenotypic data, including detailed sleep assessments, within large-scale databases, and for the application of AI and ML models to identify distinct sleep–biomarker clusters for targeted interventions. Together, these approaches offer a holistic view of the sleep–AD interface, bridging neurobiological insights with precision medicine strategies. We hope this review provides an increased incentive for clinicians to monitor and treat subjects with sleep disturbances as a modifiable risk factor for AD, and encourages large-scale clinical trials focused on using personalized sleep treatment approaches to reduce the rate, severity, and consequences of dementia in the general population.

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Data Availability No patient data is used in this review.

Declarations

Competing interests B.A.M. has served on global advisory boards for Eisai co., Ltd., and serves on a scientific advisory board for AstronauTx, Ltd. Other authors declare no conflicts of interest.

Ethics and Consent to Participate declarations Not applicable.

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